UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/721,763	11/26/2003	Eiji Mori	081356-0207	6356

22428 7590 09/27/2007

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
09/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/721,763	MORI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/9/07 amd 9/14/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-104 and 108-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-104 and 108-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Interpretation

A "monomer antibody" as compared to an "antibody polymer" is being interpreted by the Examiner as meaning the monomer is not crosslinked or bound to another substance, including another antibody, while an antibody polymer is an antibody which is necessarily crosslinked to another substance, such as a secondary antibody. This interpretation is supported by the substitute specification on page 21.

Response to Arguments

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims and Applicants' arguments; however, a new rejection due to the amendment to the claims appears below.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The translation of the certified priority documents has been received.

Claim Objections

Claims 64, 74, 79, 84, 94, 100, 101 and 108-112 are objected to because of the following informalities:

Claims 64, 69, 74, 79 and 109-112 are confusing because they recite in step (1) "Preparing Colo205 cells (ATCC No.CCL-222) which were colon carcinoma cells," but the Colo205 are still considered carcinoma cells. It is suggested that "were" be changed to "are".

Claim 74, step (2), line 6, is confusing because it recites, "such that a concentration is ...." It is not clear what the concentration is of, however, if "the" were substituted for "a", then it would be clear the control antibody concentration is being referred to.

In claims 64 and 109-112, line 4 of step (4), "calculates" should be --calculated--. In claim 79, the last line of step (2), "a" before "fresh" does not make sense.

The way claims 74, 79, 84, 94, 100, 101 are phrased: "A monoclonal antibody...binding to TRAIL-R2 and induces apoptosis in carcinoma cells...," means the monoclonal antibody must be currently bound or in the immediate process of binding to TRAIL-R2. This does not appear to Applicants' intention. Applicants' are directed to the first 3 lines of claim 89 for clear wording: "A monoclonal antibody...which binds to TRAIL-R2 and induces apoptosis...."

Claim 108 repeatedly recites "a step of", which is unnecessary and confusing since it is not "the" step of for each part. It is suggested that all occurrences of "a step of" deleted.

Claim 108 in line 1 of step (iii) recites, "the monoclonal antibodies which is a single substance". "Antibodies" is plural but "is" is singular.

Claim 108 in line 2 of step (iii) recites, "binding to TRAIL-R2 and induce apoptosis". This is grammatically incorrect and should be --binds to TRAIL-R2 and induces apoptosis--.

Claim 108, step (iv), should have a comma after the first occurrence of "antibody" and after "TRAIL-R2", and no comma after "polymer" and "bind" should be --binds--.

In claim 109, line 2, "include" should be --includes--.

Claims 109-112 have the following typographical error: in the last line it says "the antibody having the survival rate of 80%"; however, it is the cells not the antibody with the survival rate.

Appropriate correction is required.

Applicants are highly encouraged to review all the claims for consistency of language. As the claims are currently written, many different wordings are used which make the claim set as a whole incongruous and slightly confusing.

Specification

The amendment filed 6/7/04 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Examples 17-31, everything relating to Figures 12-20, every reference to monomer and exogenous factors.

Applicants are required to cancel the new matter in the reply to this Office Action.

Applicants argue that the preliminary amendment was filed concurrently with a new substitute specification on Nov. 28, 2003, corresponding to the inventor declaration requesting a priority date of Nov. 28, 2003, for the completed application, as opposed to Nov. 26, 2003. The argument has been fully considered, but is not persuasive. The original specification (93 pages) and drawings (13 pages) were filed 11/26/03. While the inventor declaration says a preliminary amendment and substitutes specification was filed 11/28/2003, nothing is of record as being received on that day. The records of the Office (viewable through PAIR) show only original submissions on 11/26/03, with the next submissions 6/7/04, and no submissions between those dates. The new matter in question was submitted 6/7/04. Therefore, whether the filing date is 11/26/03 or 11/28/03, it appears the new matter was added after the filing date. It is suggested, however, that because most or all of the matter sought to be entered in the instant application appeared in PCT/JP02/04816, of which the instant application is a CIP and the contents of which were incorporated by reference in the Transmittal of New Application Letter filed 11/26/03, that Applicants request the information be added based on incorporation by reference.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-107 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 63-107 were added 6/7/04 when the substitute specification was submitted. As originally filed, there is insufficient support in the specification for the limitations in these claims (see the above objection to the specification for a means of obviating this rejection).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64, 69, 74, 79, 84, 89, 109-112 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64, 69, 74, 79, 109-112 are indefinite because they recite in step (2) adding "the antibody or the function fragment thereof which is bound to TRAIL-R2 dissolved in RPMI-1640 medium...." This limitation creates two problems. First, if the antibody or fragment is already bound to TRAIL-R2 in medium (*i.e.,* TRAIL-R2 that is not membrane bound), then the antibody or fragment would not bind the carcinoma cells expressing TRAIL-R2 because the antibody would be "preabsorbed" as it is already abound to TRAIL-R2 prior to it be introduced to the cells. Therefore, the test for survival is not proper since according to the claims, no free antibody is left to induce apoptosis. This amounts to an incomplete method step. Second, there is insufficient antecedent basis for the antibody or fragment thereof bound to TRAIL, since the preamble says only that the antibody of fragment "binds to TRAIL-R2", not that it is bound to TRAIL-R2.

Claim 69 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: measuring survival without using the claimed antibody. Step 4 describes how survival rate is calculated, but has no measurement of a well containing carcinoma cells and said monoclonal antibody or functional fragment thereof.

Claims 89 and 94 also lack sufficient antecedent basis for "bound to TRAIL-R2 in the fourth line from the bottom for the same reason, that is, the preamble says only that the antibody of fragment "binds to TRAIL-R2", not that it is bound to TRAIL-R2.

Claims 64, 69, 74, 109-112 recite multiple times in step (4) "containing carcinoma cells". This phrase renders the claim indefinite because it is unclear if these are the Colo205 carcinoma cells. This rejection could be obviated by adding the word "said" after "containing".

Claims 84 and 89 also recites "carcinoma cells" multiple times, but it is not clear if they are the "carcinoma cells expressing TRAIL-R2". Addition of the word "said" before "containing" would obviate this rejection. If the cells are not the ones expressing TRAIL-R2, the method does not function.

Claim 89 recites the limitation "bound to TRAIL-R2" in the second and fourth lines from the bottom. There is insufficient antecedent basis for this limitation in the claim. The claim previously recited "which binds to TRAIL-R2". Replacement of "bound to" with "which binds to" would obviate this rejection.

Claim 108 is indefinite because having deleted the phrase "having the antigenicity", the term "fragment" is unmodified. The specification especially discusses an "extracellular" fragment of TRAIL-R2, which indeed is the only fragment usable to make the claimed antibody that when added to a well of cells could induce apoptosis of the cells. Therefore, it is suggested that the claim could be clarified by replacing "a fragment thereof" with --an extracellular fragment thereof--.

Claim 111 is indefinite because step (2) recites using "an" antibody which is bound to TRAIL-R2. This antibody is distinct from the monoclonal antibody of claim 108 and so the test using it has nothing to do with the method of claim 108.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
> The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 63-104 and 108 remain rejected under 35 U.S.C. 102(b) as being anticipated by Griffith et al. (J. Immunol., 162:2597, 1999; A16, IDS filed by Applicants 6/7/04) for the reasons set forth in the previous Office action and for the following reasons addressing the amendments to the claims: Even though the claims have been amended to specify that the antibody induces apoptosis when it is not a polymer, the M413 antibody of Griffith also induces apoptosis in carcinoma cells (WM9) when not crosslinked, *i.e.*, when it is not polymeric.

Griffith et al. teach monoclonal antibody M413 to DR5 (a.k.a. TRAIL-R2) that induces apoptosis in cells, including human melanoma cancer cells (Figs. 2-3). Further, Figure 2 shows that at least for WM 9 cells, soluble M413, which is not crosslinked (*i.e.*, which induces apoptosis in carcinoma cells expression a TRAIL receptor independent of exogenous factors), induces cell death in human melanoma cells at a concentration less than 1 μg/ml. Also, soluble M413 was able to inhibit TRAIL-induced cell death (Fig. 5). The antibody of Griffith et al. was purified by protein A affinity chromatography (p. 2598, end of first paragraph). It was produced by immunizing an animal with a TRAIL-R extracellular domain, obtaining antibodies from the animal, testing for apoptosis-inducing activity of the antibody on carcinoma cells, selection of antibodies with that activity and column chromatography purification (see first paragraph of p. 2598).

Griffith et al. are silent with respect to the % cell survival at the concentration specified in the instant claims in Colo205 cells, but it appears, absent evidence to the contrary, that antibody M413 has the required functional properties required by the instant claims.

Applicants argue that Griffith teaches away from the instant invention because Griffith et al. state that "...TRAIL-R1 or -R2 ligation does not always lead to death," and "...multiple factors function together to provide resistance against the cytotoxic effects of TRAIL." The argument has been fully considered, but is not persuasive. When the authors referred to the complexity of TRAIL-induced cell death, they were referring to the presence or absence of four independent TRAIL receptors as well as the TRAIL-resistance of certain cells. This in no way takes away from the effect of the apoptosis-inducing antibody M413 on carcinoma cells in the absence of crosslinking. What it means is that the property of the cell tested, which TRAIL receptors the cell expresses and the specificity of the antibody(ies) used will determine whether

and how much apoptosis the antibody induces. Second, the resistance against cytotoxicity does not teach away from the action of antibody M413. In TRAIL-sensitive cells, the antibody induces apoptosis. In TRAIL-resistant cells, it may be necessary to convert the cells into TRAIL-sensitive cells with a compound such as Act D in order for the anti-TRAIL-R2 antibody to be able to induce apoptosis.

Applicants argue that Griffith does not teach a monomeric agent that, by itself, induces apoptosis *via* binding TRAIL-R2. The argument has been fully considered, but is not persuasive. As stated in the rejection, anti-TRAIL-R2 monoclonal antibody M413 induced apoptosis without crosslinking (*i.e.*, when soluble or monomeric) in WM9 carcinoma cells at a concentration less than 1000ng/ml (Fig. 2). Cell survival was about 80%, however, these cells were not Colo205 cells and were in approximately .350 ml (the average 96-well plate used has a capacity of about 350µl). There were only 10,000 cells/well compared to 17,500 cells/.35ml recited in some of the instant claims (*e.g.*, claim 89). Therefore, on might expect a higher survival rate of WM 9 cells due to the reduced density and number of cells tested by Griffith. While it is not possible to directly compare the results of melanoma cells (Griffith) to Colo205 cells (*e.g.*, Example 28 of specification), antibody M413 reasonably appears to meet the limitations of the claims.

Claims 63-104 and 108 remain rejected under 35 U.S.C. 102(e) as being anticipated by US 6,342,369 for the reasons set forth in the previous Office action and for the following reasons addressing the amendments to the claims: Even though the claims have been amended to specify that the antibody induces apoptosis when it is not a polymer, the 16E2 antibody also induces apoptosis in carcinoma cells (SK-MES-1) when not crosslinked, *i.e.*, when it is not polymeric.

US 6,342,369 teaches antibody 16E2, which has *in vitro* cell death-inducing activity in the absence of crosslinking at concentrations less than 1 µg/ml as shown in Figure 13C, where it had agonistic, *i.e.*, apoptotic, activity at a concentration of 0.4 µg/ml for SK-MES-1 (human lung carcinoma cell line cells, col. 53, lines 8-9) when not crosslinked. The antibody was produced by immunizing an animal with a TRAIL-R extracellular domain, obtaining antibodies from the animal, testing for apoptosis-inducing activity of the antibody on carcinoma cells, selection of antibodies with that activity and column chromatography purification (see Example 9).

US 6,342,369 did not use the same assay used to characterize the claimed antibody in the instant claims, but it appears absent evidence to the contrary that antibody 16E2 has the required functional properties required by the instant claims.

Applicants' current attempt to compare the antibodies of US 6,342,369 and US 2003/0190687 (US 7,244,429, which receives a priority date of 60/201,344, filed 5/2/00) in experiments to allow more direct comparison to the claimed antibodies is acknowledged.

Applicants argue that, "In fact, the '369 patent does *not* describe an antibody that is "a single substance" that binds to TRAIL-R2 receptors that are expressed in carcinoma cells and thereby induces death of those cancerous cells." The argument has been fully considered, but is not persuasive. Because the patent teaches that antibody 16E2 in the absence of crosslinking induced apoptosis in lung carcinoma cells (SK-MES-1, see Figure 13C) . In col. 53, line 26, it says, "Wells not receiving a crosslinking antibody received media alone." In line 51 it says, "As shown in FIGS. 13C and 14B, the 16E2 and 20E6 antibodies agonistically induced apoptosis in SK-MES-1 cells."

It is noted that while antibody 16E2 is a single chain antibody, it appears to meet the limitation of a functional fragment of a monoclonal antibody.

Claims 63-104 and 108 remain rejected under 35 U.S.C. 102(e) or 102(a) as being anticipated by US 2003/0190687, which will now be referred to as US 7,244,429, for the reasons set forth in the previous Office action and for the following reasons addressing the amendments to the claims: Even though the claims have been amended to specify that the antibody induces apoptosis when it is not a polymer, the TRA-8 antibody also induces apoptosis in carcinoma cells (Jurkat leukemia cells) when not crosslinked, *i.e.*, when it is not polymeric.

US 7,244,429 teaches TRA-8 antibody to TRAIL-R2. The antibody induces apoptosis in carcinoma cells (see, for example, Example 8 and Figures 2c, 3b). The antibody was produced by immunizing an animal with a TRAIL-R extracellular domain, obtaining antibodies from the animal, testing for apoptosis-inducing activity of the antibody on carcinoma cells, selection of antibodies with that activity and column chromatography purification (see Examples 2 and 3).

TRA-8 appears to have all the properties, absent evidence to the contrary, of the instantly claimed antibodies.

Applicants state that "their preliminary experiments indicate that TRA-8 cannot induce apoptosis "as a single substance without forming a polymer."" The Examiner cannot comment on Applicants' results, as they have not yet been presented. However, they seem to contradict the specification of US 7,244,429, which states in col. 30 beginning line 50 that, "Further functional analysis using human Jurkat cells as targets showed that, in the absence of crosslinking, TRA-8 strongly induces cell death, demonstrated by three different assays for cell viability including ATPLite, MTT and PI exclusion (FIG. 1e). Greater than 50% of Jurkat cells are killed by nanogram levels of TRA-8 as shown by ATPLite assay. The killing activity of TRA-8 is specific for DR5 as it could be blocked by DR5-Ig but not DR4-Ig fusion protein (data not shown)."

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873.

Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
September 18, 2007

LORRAINE SPECTOR
PRIMARY EXAMINER